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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,341	HAYDEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005 and 08 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-40 and 42-57* is/are pending in the application.

4a) Of the above claim(s) *52-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-40 and 42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 9/12/2005, in which claims 1-34 and 41 were canceled; and claims 35-37, 40, 43, 45 and 46 were amended. Currently, claims 35-40 and 42-57 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II and the disease hyperlipidemia with traverse in the reply filed on 9/23/2004. Claim 37 was previously withdrawn from consideration as reading on a non-elected disease. Claim 37 has been amended such that it now reads on the elected disease. Currently, claims 35-40 and 42-51 are readable upon the elected invention.

Claims 52-57 are withdrawn from further consideration, as being drawn to a nonelected invention.

Information Disclosure Statement

Receipt of an information disclosure statement (IDS), filed on 9/30/2002, is acknowledged. The signed and initialed PTO 1449 was mailed 11/19/2004; however, pages 11-14 of the IDS were not considered. Pages 11-14 have been considered and mailed herewith. Non-initialed references were not considered because the references were large volumes of work and relevant page numbers within the publication were not provided (see 37 CFR § 1.98(b)).

Sequence Compliance

The statement provided with the paper copy and computer readable form of the sequence listing on 2/8/2006 does not state that the content of the paper and computer readable copies are the same and include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). In response to this Office action, Applicant must provide the required statement.

Response to Arguments - Claim Objections

The objection of claims 35, 40, 43, 45 and 46 has been withdrawn in view of Applicant's amendment to the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35, 36, 38, 39, 42-44, 47, 48 and 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S.

Patent No. 6,814,962 (hereafter '962) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989; see the entire reference). This rejection was made in the Office action mailed 11/19/2004 and is reiterated below.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

In the instant case, claims 1-6 of the '962 patent recite methods of treating dyslipoproteinaemia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, familial hypertriglyceridaemia, and combined familial hyperlipidaemia and postprandial hyperlipidaemia comprising administering to the patient a defective recombinant adenovirus comprising a nucleic acid sequence coding for a biologically active human lipoprotein lipase (LPL). The claims of the '962 patent differ from claims 35, 36, 38, 39, 42-44, 47, 48 and 51 of the instant application in that they fail to disclose the use of a nucleic acid sequence encoding the S447X variant of human LPL.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2

legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the enclosed alignment, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of 2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

Therefore, it would have been obvious to modify the method of claims 1-6 of the '962 patent to include the S447X nucleic acid sequence taught by Kozaki et al because the claims recite the use of a nucleic acid encoding a biologically active human LPL and Kozaki et al teach that the S447X truncation is a functional LPL protein. One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity as taught by Kozaki et al.

Response to Arguments - Double Patenting

Applicant's arguments filed 9/12/2005 have been fully considered but they are not persuasive.

The response essentially asserts that there is no teaching or suggestion in the cited art that would serve as a basis for a reasonable expectation that LPL S447X therapeutics could be used to treat hyperlipidemia in an amount effective to lower triglycerides and to raise HDL-C. The response points to a statement made by Kozaki et al: "further studies are required to know the effect of the Ser447 to stop mutation."

The remarks are not found persuasive, because the ability of LPL S447X to lower triglycerides and to raids HDL-C is an inherent property of the protein. Kozaki et al state, "The overall and specific activities of the Ser^{447} → stop mutant were about twice as high as those of normal LPL in medium (Figs. 3 and 4), and the results were faithfully reproducible in nine experiments." See page 1771, left column, lines 6-10. Furthermore, the prior art teaches that humans homozygous for the LPL S447X variant have lower plasma triglycerides and higher HDL-C as compared to noncarriers (Wittrup et al. Circulation. Vol. 99, pages 2901-2907, June 8, 1999, e.g. page 2903, left column; Groenemeijer et al. Circulation. Vol. 95, pages 2628-2635, 1997; e.g. paragraph bridging pages 5/20-6/20). Around the time the invention was made, it was recognized that the S447X variant might result in increased production of LPL protein and higher lipolytic activity (Gagne et al. Clin Genet. Vol. 55, pages 450-454, June 1999; e.g. paragraph bridging pages 452-453). Thus, the S447X variant of LPL was known to have a protective effect *in vivo*, including increasing HDL-C.

Accordingly, one would expect the LPL S447X therapeutic to treat hyperlipidemia in an amount effective to lower triglycerides and to raise HDL-C. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. This is a new rejection, necessitated by the amendment to the claims in the reply filed 9/12/2005.

Claim 46 depends from canceled claim 41. Canceled claim 41 was drawn to the claimed method, wherein the nucleic acid "hybridizes under stringent conditions" to nucleotides 256-1599 of SEQ ID NO: 4. The specification does not define the term stringent conditions and one would not be reasonably apprised of the scope of the invention. Claim 46 is an incomplete claim. It would be remedial to amend the claim to depend from a pending claim.

Claim 50 depends from claim 46 and is indefinite for the same reasons as applied to claim 46.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-40, 42-45, 47-50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hyperlipidemia associated with LPL or ApoE deficiency, comprising the administration of an adenoviral vector containing the coding sequence for an LPL S447X protein, does not reasonably provide enablement for the treatment of any other conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This grounds of rejection has been rewritten to address the amendments to the claims in the reply filed 9/12/2005 and has been extended to amended claim 37. This rejection has been combined with the previous rejection of

claims 40, 41, 45, 46, 49 and 50 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The sequence listing submitted on 2/8/2006 now provides an LPL coding sequence for SEQ ID NO: 4, and thus altered the scope of the claims. The amendments to the claims and sequence listing necessitated the extension of the rejection to claims 37, 40, 41, 45, 46, 49 and 50.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention and breadth of the claims: The claims are drawn to a method of treating hyperlipidemia in a subject, comprising administering to the subject an effective amount of a nucleic acid encoding an LPL S447X protein (i.e. gene therapy) effective to lower triglycerides and to raise HDL-C. Claim 36 limits the hyperlipidemia to one that is associated with LPL or ApoE deficiency. Claim 37 limits the hyperlipidemia to one that is associated with complete LPL deficiency. The claims encompass the use of any vector or any viral vector to administer the nucleic acid.

The nature of the invention is complex in that lipid metabolism is a highly complex process with multiple genetic and environmental modifiers contributing to the health of the individual.

Guidance of the specification and existence of working examples: The present specification provides little or no guidance to support the claimed invention for gene therapy

applications other than for the reduction in triglyceride and cholesterol levels and raise HDL-C in LPL deficient heterozygotes and homozygotes, and ApoE deficient homozygotes (e.g. Example 2). Although Applicant has demonstrated an increase in LPL activity subsequent to the administration of an adenovirus carrying the LPL S447X coding sequence, there is no support in the specification to indicate that an increase in LPL activity is sufficient to treat the disclosed LPL-responsive conditions.

The working examples disclose adenovirus-mediated gene transfer of the human LPL S447X coding sequence (i.e. Ad-447) to LPL +/-, LPL-/- and ApoE-/- mice (Examples 1, 2 and 5). The administration of Ad-447 to these mice resulted in a reduction of total and HDL cholesterol and triglyceride levels and an increase in HDL-C. Thus, these examples demonstrate that the expression of LPL results in a decrease in hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) in mice with this specific genetic background.

Further, the working examples disclose a genetic association of the LPL S447X genotype with the New York Heart Association (NYHA) classification for prescription of activity for cardiac patients and with protection against coronary heart disease (Examples 3 and 4).

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of support for a broad class of diseases treatable by the administration of an LPL nucleic acid. Adenoviral-mediated gene transfer of the human LPL coding sequence was shown to result in decreased triglyceride levels in LPL -/-, ApoE -/-, LDL receptor (LDLr) and hepatic lipase (HL) -/- mice, decreased plasma cholesterol in ApoE-/-, LDLr -/-, and HL -/- mice, and decreased phospholipid concentrations in HL-/- mice (Excoffon et al, e.g. page 2535, right column; Kobayashi et al, e.g. Table II; Zsigmond et al, Human Gene

Therapy, Vol. 8, pages 1921-1933, 1997, e.g. Table 1). In a post filing review of the art, Mead et al acknowledge that LPL has been directly or directly implicated in several pathophysiological conditions that are characterized by marked hypertriglyceridemia, including chylomicronaemia, cachexia, insulin resistance and diabetes, obesity and atherosclerosis (Mead et al., J. Mol. Med., Vol. 80, pages 753-769, 2002; e.g. page 760, left column, paragraph 3). Regarding chylomicronaemia, Mead et al note that in addition to a deficiency in LPL, this condition can result from a deficiency of the LPL cofactor apoC2 (e.g. page 760, right column, paragraph 1). Thus, if an individual lacks the necessary cofactors for LPL function, then that individual cannot be treated for chylomicronaemia by increasing the level of LPL. Further, obesity and atherosclerosis are multifactorial diseases, in which the role of LPL is not clear (e.g. page 760-761, *Obesity* and *Atherosclerosis*). While this reference indicates the promise of gene therapy, it will require further research before becoming a reality (e.g. page 763, left column).

Regarding the use of genetic association to determine the therapeutic potential of a gene product, Page et al (Am. J. Hum. Genet. Vol. 73, pages 711-719, 2003) state that "there is no explicit consensus about what constitutes sufficient evidence to establish causation from association" (see the paragraph bridging pages 711-712). Further, Page et al note that a p-value of less than 0.05 is useful to reduce the rate of false positives, but it is only one component in a set of criteria for causation (see the paragraph bridging pages 713-714). Thus, a single experiment demonstrating an association does not prove causation or the ability to treat an individual with the associated gene product.

In a review on the current status of gene therapy, the continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-

viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While the two references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Luo et al, p. 33, col. 1, 1st paragraph.

Predictability of the art: The area of the invention is unpredictable. In 1999, the administration of an E1 and E4 deleted human adenovirus type 5 vector to an 18-year-old individual unexpectedly resulted in the death of the individual (Edelstein et al, The Journal of Gene Medicine, Vol. 6, pages 597-602; e.g. page 599, The hopes and the setbacks). Further, in 2000, the administration of a retrovirus vector resulted in two of ten children developing a leukemia-like condition from the integration of the vector near the LMO2 proto-oncogene promoter (e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the full scope of the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine whether the effect of LPL expression could be exploited for treatment of a disease,

how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the full scope of the claimed invention.

Response to Arguments - 35 USC § 112

The rejection of claim 41 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claims.

Applicant's arguments filed 9/12/2005 have been fully considered but they are not persuasive. The response asserts that SEQ ID NO: 4 has been corrected to reflect the sequence of Figure 4, which has been confirmed to correspond to the cited GenBank reference. Further, the response asserts that the claims as amended are fully enabled by the specification based upon the examiner's acknowledgement that the specification is enabling for methods of treating hyperlipidemia associated with LPL or ApoE deficiency, comprising the administration of an adenoviral vector containing the coding sequence for an LPL S447X protein. The sequence of SEQ ID NO: 4 has been corrected such that it encodes a human wild type lipoprotein lipase. However, the arguments are not found persuasive, because the claims have not been amended to claim subject matter commensurate in scope with the enabled subject matter indicated in the

rejection set forth on pages 10-15 of the Office action mailed 11/19/2004. Given the unpredictable nature of gene delivery using non-viral systems or viral systems such as retroviral vectors, at the time the invention was made, one would have been required to conduct an undue amount of experimentation to practice the full scope of the claimed invention. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-39, 42-44, 47, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al (WO 96/11276; see the entire reference) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989; see the entire reference). This rejection was made in the Office action mailed 11/19/2004 and has been extended to claims 37, 40, 45 and 49. Claim 37 was amended, in the reply filed 9/12/2005, to read on the elected disease, hyperlipidemia. The sequence listing submitted on 2/8/2006 now provides an LPL coding sequence for SEQ ID NO: 4, and thus altered the scope of the claims. The amendment to the claims and sequence listing necessitated the extension of the rejection to claims 37, 40, 45 and 49.

Hayden et al teach the *in vivo* transduction of human cells with viral gene therapy vectors comprising the full-length LPL cDNA sequence for the treatment of hypertriglyceridemia (i.e. one form of hyperlipidemia) resulting from heterozygous or homozygous LPL deficiency (e.g. page 11, lines 10-31; page 12, lines 1-31).

Hayden et al do not teach the administration of a S447X LPL cDNA sequence.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446). Moreover, Kozaki et al suggest that the S447X mutation may have some protective effect against the development of hypertriglyceridemia (e.g. page 1771, left column, paragraph 1).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X RNA with at least 90% identity to nucleotides 256 through 1599 of SEQ ID NO: 4 and encodes a protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2 legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the enclosed alignment, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of 2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the viral gene therapy vector of Hayden et al to include the S447X nucleic

acid sequence taught by Kozaki et al in place of the wild type LPL sequence because Hayden et al teach it is within the ordinary skill in the art to use an LPL coding sequence in the viral gene therapy vector for the treatment of hyperlipidemia associated with LPL deficiency and Kozaki et al teach that the S447X truncation is a functional LPL protein.

One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity and a protective effect against the development of hypertriglyceridemia as taught by Kozaki et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

Applicant's arguments filed 9/12/2005 have been fully considered but they are not persuasive.

The response essentially asserts that there is no teaching or suggestion in the cited art that would serve as a basis for a reasonable expectation that LPL S447X therapeutics could be used to treat hyperlipidemia in an amount effective to lower triglycerides and to raise HDL-C. The response points to a statement made by Kozaki et al: "further studies are required to know the effect of the Ser447 to stop mutation."

The remarks are not found persuasive, because the ability of LPL S447X to lower triglycerides and to raids HDL-C is an inherent property of the protein. Kozaki et al state, "The overall and specific activities of the Ser^{447} → stop mutant were about twice as high as those of normal LPL in medium (Figs. 3 and 4), and the results were faithfully reproducible in nine

experiments." See page 1771, left column, lines 6-10. Furthermore, the prior art teaches that humans homozygous for the LPL S447X variant have lower plasma triglycerides and higher HDL-C as compared to noncarriers (Wittrup et al. Circulation. Vol. 99, pages 2901-2907, June 8, 1999, e.g. page 2903, left column; Groenemeijer et al. Circulation. Vol. 95, pages 2628-2635, 1997; e.g. paragraph bridging pages 5/20-6/20). Around the time the invention was made, it was recognized that the S447X variant might result in increased production of LPL protein and higher lipolytic activity (Gagne et al. Clin Genet. Vol. 55, pages 450-454, June 1999; e.g. paragraph bridging pages 452-453). Thus, the S447X variant of LPL was known to have a protective effect *in vivo*, including increasing HDL-C.

Accordingly, one would expect the LPL S447X therapeutic to treat hyperlipidemia in an amount effective to lower triglycerides and to raise HDL-C. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER